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# Hexabromocyclododecanes (HBCDs) in the Environment and Humans: A Review

ADRIAN COVACI,<sup>\*,†</sup> ANDREAS C. GERECKE,<sup>‡</sup>  
ROBIN J. LAW,<sup>§</sup> STEFAN VOORSPOELS,<sup>†</sup>  
MARTIN KOHLER,<sup>‡</sup> NORBERT V. HEEB,<sup>‡</sup>  
HEATHER LESLIE,<sup>⊥</sup> COLLIN R. ALLCHIN,<sup>§</sup> AND  
JACOB DE BOER<sup>⊥</sup>

*Toxicological Centre, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium, Swiss Federal Laboratories for Materials Testing and Research (Empa), Dübendorf, Switzerland, The Centre for Environment, Fisheries and Aquaculture Science, Burnham, United Kingdom, and The Netherlands Institute for Fisheries Research, University of Wageningen, IJmuiden, The Netherlands*

Hexabromocyclododecanes (HBCDs) are brominated aliphatic cyclic hydrocarbons used as flame retardants in thermal insulation building materials, upholstery textiles, and electronics. As a result of their widespread use and their physical and chemical properties, HBCDs are now ubiquitous contaminants in the environment and humans. This review summarizes HBCD concentrations in several environmental compartments and analyzes these data in terms of point sources versus diffuse sources, biomagnification potential, stereoisomer profiles, time trends, and global distribution. Generally, higher concentrations were measured in samples (air, sediment, and fish) collected near point sources (plants producing or processing HBCDs), while lower concentrations were recorded in samples from locations with no obvious sources of HBCDs. High concentrations were measured in top predators, such as marine mammals and birds of prey (up to 9600 and 19 200 ng/g lipid weight, respectively), suggesting a biomagnification potential for HBCDs. Relatively low HBCD concentrations were reported in the few human studies conducted to date (median values varied between 0.35 and 1.1 ng/g lipid weight). HBCD levels in biota are increasing slowly and seem to reflect the local market demand. One important observation is the shift from the high percentage of the  $\gamma$ -HBCD stereoisomer in the technical products to a dominance of the  $\alpha$ -HBCD stereoisomer in biological samples. A combination of factors such as variations in solubility, partitioning behavior, uptake, and, possibly, selective metabolism of individual isomers may explain the observed changes in stereoisomer patterns. Recommendations for further work include research on how HBCDs are transferred from products into the environment upon production, use, and disposal. Time trends need to be analyzed more in detail, including HBCD stereoisomers, and more data on terrestrial organisms are needed, especially for humans. Whenever possible, HBCDs should be

analyzed as individual stereoisomers in order to address their fate and effects.

## Introduction

Hexabromocyclododecanes (HBCDs) are additive brominated flame retardants (BFRs) applied in extruded and high-impact polystyrene foams (up to 2.5% HBCDs) which are used as thermal insulation in buildings, in upholstery textiles (6–15% HBCDs), and to a minor extent in electrical equipment housings (1). In 2001, the world market demand for HBCDs was 16 700 metric tons, from which 9500 metric tons were sold in the European Union (2). These figures make HBCD the second highest-volume BFR used in Europe, after tetrabromobisphenol-A (TBBP-A) and before decabromodiphenyl ether (1). Recently, the production and use of penta- and octabromodiphenyl ethers has been restricted in Europe (3). HBCDs may be used as an alternative for polybrominated diphenyl ethers (PBDEs) in some applications (4). To date, there are no restrictions on the production or use of HBCDs.

Like PBDEs, HBCDs can enter the environment by a number of different pathways, such as emission during production of BFRs or the manufacture of flame-retarded products, by leaching from consumer products, or following disposal. HBCDs were first detected in fish and sediment samples from the river Viskan in Sweden (4) and, since then, their presence has been reported in a wide variety of biota and abiotic environmental samples.

In comparison to PBDEs, the toxicological database for HBCDs is still limited. Acute toxic effects appear to be low (5). However, there are indications that oral exposure to HBCDs induces drug-metabolizing enzymes in rats, such as hepatic cytochrome P450 (CYP) (6), and that HBCDs may induce cancer by a nonmutagenic mechanism (7, 8). There are reports that HBCDs can disrupt the thyroid hormone system (5) and affect the thyroid hormone receptor-mediated gene expression (9). Following neonatal exposure experiments in rats, developmental neurotoxic effects can be induced, such as aberrations in spontaneous behavior, learning, and memory function (10). HBCDs can also alter the normal uptake of neurotransmitters in rat brain (11). Further research on the actual levels at which these effects occur is needed.

The European Union risk assessment for HBCDs began in 1997, and it is expected to be completed during 2006. In

\* Corresponding author phone: +32 3 8202704; fax: +32 3 8202722; e-mail: adrian.covaci@ua.ac.be.

<sup>†</sup> University of Antwerp.

<sup>‡</sup> Swiss Federal Laboratories for Materials Testing and Research.

<sup>§</sup> The Centre for Environment, Fisheries and Aquaculture Science.

<sup>⊥</sup> University of Wageningen.

its current draft version, this risk assessment concludes that there are needs for further information (12). During the period of the preparation of this risk assessment, the BFR industry in Europe took voluntary measures to reduce the emission of HBCDs from production and handling sites. However, these measures do not imply any emission reduction during the use or disposal of products in which HBCDs are used. HBCDs have been identified by the U.K. Chemical Stakeholders Forum as persistent, bioaccumulative, and toxic chemicals and are included on the OSPAR list of chemicals for priority action (12). While currently no specific regulatory actions are taken in the United States, HBCDs have been identified for risk assessment in Canada, Australia, and Japan. Further regulatory/assessment activities in these countries will take place over the next few years. In the meantime, the manufactured and imported amounts of HBCDs must be reported to the governmental institutions (12).

This present review adds to a recently published article and response to comments (13, 14) and aims to summarize the current state of knowledge about the distribution and levels of HBCDs in various environmental compartments, whenever possible given as individual stereoisomers. HBCDs can be considered as emerging contaminants, which is reflected in the currently rather limited, but continuously growing, data set. Consequently, data gaps will be identified and discussed.

**Chemical and Physical Properties.** Technical grade HBCD mixtures are obtained via bromination of cyclododeca-1,5,9-triene isomers. Six stereogenic centers at positions 1,2,5,6,9, and 10 are formed, which theoretically leads to 16 stereoisomers of 1,2,5,6,9,10-hexabromocyclododecane: six pairs of enantiomers and four meso forms (15). The commercial mixtures mainly consist of  $\gamma$ -HBCD (75–89%), while  $\alpha$ -HBCD and  $\beta$ -HBCD are present in lower amounts (10–13% and 1–12%, respectively). Furthermore, at least two additional stereoisomers, named  $\delta$ - and  $\epsilon$ -HBCD, are present at minor concentrations (15). HBCDs are subject to thermal rearrangement at temperatures above 160 °C, resulting in a specific mixture of stereoisomers (78%  $\alpha$ -HBCD, 13%  $\beta$ -HBCD, and 9%  $\gamma$ -HBCD) (16). Such conditions can occur during the production or processing of materials containing HBCDs (e.g., extruded polystyrene), and therefore the relative abundance of the various HBCD stereoisomers may differ from that of the technical HBCD mixtures.

Substantial structural dissimilarities of individual HBCD stereoisomers might give rise to differences in polarity, dipole moment, and, as already found, in water solubility. Solubilities of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -HBCD in water are 48.8, 14.7, and 2.1  $\mu\text{g/L}$ , respectively (17). These differing properties may result in distinctive rates of biological uptake and metabolism and could explain the observed differences in their environmental behavior (18, 19). A relatively high octanol–water partitioning coefficient ( $\log K_{ow}$ ) of 5.6 has been estimated for HBCDs (20).

For a better understanding of the environmental fate and behavior of individual HBCDs, it is essential to have stereoisomer-specific data. Separation of different HBCD stereoisomers is not possible by gas chromatography (GC). A relatively broad, unresolved peak is obtained due to thermal rearrangement of the stereoisomers, and results reflect total HBCD concentrations (21). In contrast to GC, HBCD stereoisomers can be easily separated using reversed-phase liquid chromatography and determined by mass spectrometry (LC/MS or LC/MS-MS) (22, 23). Furthermore, several enantiomers can be resolved on a chiral, permethylated  $\beta$ -cyclodextrin stationary phase for LC (15, 24). As a consequence, up to eight individual HBCD stereoisomers can now be differentiated by LC/MS (15).

**Strategy of the Review.** All available literature on HBCD concentrations in the environment and humans, published

until December 2005 in peer-reviewed scientific journals, conference proceedings, or official reports found on the Internet, was acquired and classified. Articles on the toxicology and metabolism of HBCDs were not included. Although several reviews are available for BFRs in general (18, 19, 25, 26), information on HBCDs specifically is often “lost” in the greater dataset available for PBDEs. Therefore, we identified a stringent need for a comprehensive review on HBCDs in which current levels and temporal and spatial trends in concentrations are analyzed and recommendations for further research are given. A similar review is already available for PBDEs (27).

Both GC and LC data for HBCDs were used in this review, and so the results are presented as both total HBCDs and in a stereoisomer-specific form when available. For comparative purposes, all results were expressed on a lipid weight (lw) basis. Some results originally expressed as wet weight (ww) were recalculated in order to make the units consistent. Arithmetic means were presented for each data set, since these values have often been reported in the original papers or could easily be calculated from the original data. Results below the limit of quantification (LOQ) were substituted by a value equal to the LOQ, which was further used for the calculation of arithmetic means. If the date of sample collection was not given, it was assumed that the samples were taken 2 years before the publication date of the results.

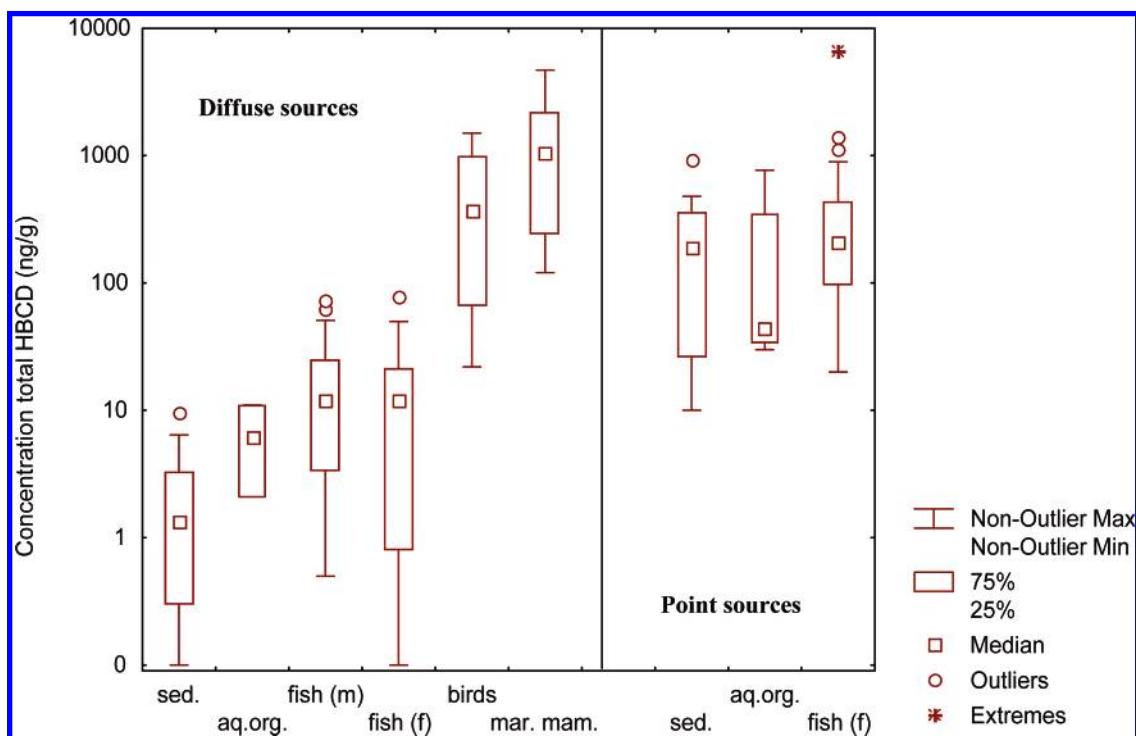
The results of recent round robin studies (QUASIMEME Laboratory Performance Studies, see [www.quasimeme.org](http://www.quasimeme.org)) on the determination of HBCDs in environmental samples demonstrated that the precise quantitative determination of HBCDs is still a demanding task. Thus, the measurements presented in this review are presumably associated with an uncertain analytical error.

## Environmental Levels

Figure 1 shows HBCD levels in various environmental compartments (data taken from the comprehensive list in tables SI 2–6 in the Supporting Information). As will be discussed in detail further below, HBCD concentrations are rising along the food chain and are also elevated in the vicinity of point sources. Please note that throughout this review, we use the expression “point sources” for production sites of HBCDs or for sites producing HBCD flame-retarded materials (downstream users). Diffuse sources include all other possible sources, such as municipal wastewater treatment plants, electronic equipment, or dismantling facilities.

**Air and Dust.** The analytical difficulties inherent to this class of compounds and the low environmental concentrations that have to be measured make HBCD data in air samples scarce. Due to the high lipophilicities and low vapor pressures of HBCDs, the majority of the airborne fraction is sorbed to particulate matter and only a minor fraction is found in the gas phase. Unfortunately, most studies did not differentiate between HBCDs in the gas-phase and the particulate fractions and focused mainly on areas suspected of high exposure, such as HBCD production plants or styrene foam manufacturing plants (12). The only data that are available for background concentrations of HBCDs originate from Scandinavian countries (18, 28, 29) and, recently, from the United States (30).

Table SI 1 in the Supporting Information summarizes all available HBCD data in air and dust. HBCDs were detected in air from both urban and rural areas in Sweden (range 2–610  $\text{pg/m}^3$ ), and also in air from remote sites in northern Sweden, Finland and the United States (18, 25, 29, 30). The levels of HBCDs in the atmosphere in remote areas can be correlated with their detection in various animals from remote areas such as Greenland and Svalbard (25, 26, 31, 32) and suggests long-range atmospheric transport of HBCDs from western Europe and eastern North America to Arctic regions.



**FIGURE 1.** Distribution of concentrations of total HBCDs in sediments (ng/g dry weight) and biological samples (ng/g lipid weight) from species situated at different levels of the food chain. Data are taken from Tables SI 2–5 in the Supporting Information. Legend to the figure: sed, sediments; aq. org., aquatic organisms; mar. mam., marine mammals; m, marine; f, freshwater.

Much higher values of HBCDs (up to 28 500 ng/m<sup>3</sup>) were measured in air from working environments at plants producing HBCDs or extruded polystyrene foam flame retarded with HBCDs (Table SI 1) (12).

HBCDs were found in all dust samples in a study conducted in offices and private homes from several EU countries (33–35), and also in private houses in the United States (36). Recently, HBCDs could be determined (at concentrations up to 58 000 ng/g dry weight) in several pooled individual home and office dust samples from Belgium (35).

No studies have been performed to date regarding the bioavailability of HBCDs following pulmonary (inhalation of air and dust) or gastro-intestinal (ingestion of dust) exposure in humans. The significance of the measured concentrations in air and dust can therefore not be assessed. Future studies focusing on bioavailability would provide more insight and may support the risk assessment of exposure to HBCDs via air and dust.

**Sediment, Soil, and Sewage Sludge.** Due to their hydrophobic character, HBCDs are strongly bound to solid particles such as soil, sediment, and sewage sludge. HBCDs could be detected in almost all studies, except for a few sediment samples taken in coastal waters and at an offshore sedimentation site (Table SI 2). Low concentrations (<10 ng/g dry weight) were found at sites without known sources of HBCDs (Table SI 2). It is highly possible that the contamination with HBCDs at these sites is due mainly to diffuse sources and long-range transport. HBCDs have sometimes been found at substantially higher concentrations than PBDEs in sediments and suspended particulate material (SPM) downstream of urban centers and industrial areas. The highest concentrations in SPMs (up to 1700 ng/g dry weight) were measured downstream of HBCD production sites (Rivers Skerne and Tees, U.K.; Western Scheldt and Scheldt basin, Belgium; 37) and of industrial users of HBCDs (River Viskan, Sweden, (4); River Cinca, Spain, 38). In other studies investigating sediments (39–46), concentrations of HBCDs were considerably lower (Table SI 2).

Soil samples collected near HBCD-processing factories (29, 47) contained high concentrations of HBCDs, ranging between 111 and 23 200 ng/g dry weight (Table SI 2).

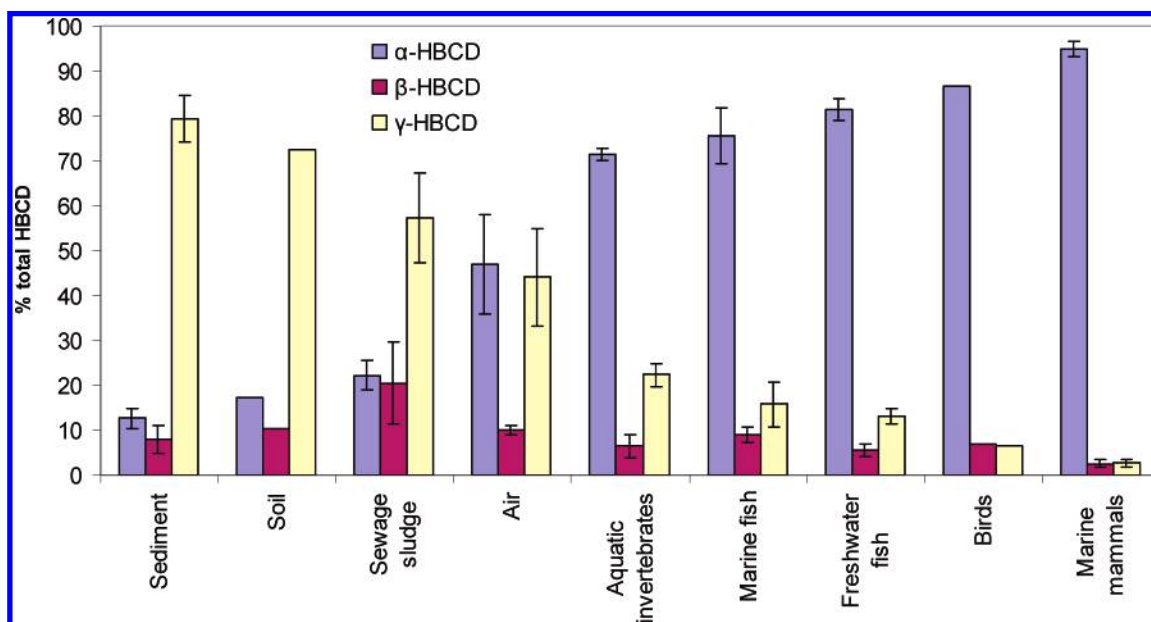
The widespread occurrence of HBCDs in sewage sludge (29, 37, 46, 48, 49) is a result of diffuse leaching and abrasion (particulates) from flame-retarded products into wastewater streams (49). Application of these sludges to agricultural or other land may redistribute the contained HBCDs to the soil/sediment compartment, and further into aquatic or terrestrial food chains, as already demonstrated for PBDEs (18, 26). HBCD concentrations in the influent of wastewater treatment plants were much higher than those in the effluent (Table SI 2), suggesting that HBCDs are largely removed from the wastewater during the treatment process.

The stereoisomeric profile of HBCDs in most sediment samples was found to be similar to that of commercial HBCD formulations, with  $\gamma$ -HBCD being the most abundant stereoisomer (37). However in some locations (37, 42, 43), the contribution of  $\alpha$ -HBCD was higher than in the technical mixture (Table SI 2). At present, it is not clear whether this difference in the composition of the HBCD stereoisomers between some sediments and technical HBCDs is caused by thermal isomerization during the processing of HBCDs or by stereoisomer-specific processes in the environment.

**Fish and Other Aquatic Organisms.** Due to their high position in the food chain and the elevated exposure in the aquatic environment, fish often exhibit high residues of contaminants. Not surprisingly, HBCDs have been detected in many studies (4, 22, 24, 29, 37, 38, 41–43, 50–62) in both freshwater and marine biota (Table SI 3).

Concentrations of HBCDs in fish downstream of an HBCD manufacturing plant on the River Skerne (Durham, U.K.) were very high, with levels up to 10 275 ng/g lw (50). In comparison to upstream reference sites, higher concentrations downstream of point sources have also been observed in the rivers Cinca (Spain), Viskan (Sweden), and Tees (U.K.) (Table SI 3). Concentrations of HBCDs were mostly between 10 and 1000 ng/g lw in urban/suburban regions of Europe,





**FIGURE 2.** Stereoisomer distribution, given as percentage of total HBCDs, averaged for samples of air, sediment, soil, sewage sludge, invertebrates, fish (marine and freshwater), marine mammals, and cormorants (Tables SI 2–5 in the Supporting Information). Data are given with increasing proportion of  $\alpha$ -HBCDs, and data variations are indicated as standard errors.

while levels in the North American Great Lakes were lower by approximately 1 order of magnitude (3–80 ng/g lw) (Table SI 3). Concentrations in fish from Swiss alpine lakes showed also lower concentrations (up to 36 ng/g lw) than fish from lakes nearby urban areas (51, 52). Concentrations of HBCDs also showed a strong regional differentiation; lower HBCD concentrations were, for example, measured in the northern Baltic compared to the Baltic Proper, suggesting ongoing inputs into the southern part of the Baltic Sea (55).

Tissue-specific accumulation differs among fish species. In barbel, bib, and whiting, HBCD concentrations were higher in liver than in muscle, while in sole and plaice, the concentrations in muscle were higher than those in liver (24, 38).

Less data exist for aquatic invertebrates. The highest concentrations (up to 730 ng/g lw) were found in starfish, shrimps, and mussels from the Rivers Tees and Scheldt, close to current or past production facilities for HBCDs (Table SI 3). However, concentrations of HBCDs in invertebrates were lower than in fish collected from corresponding locations, which suggests biomagnification.

In contrast to sediments,  $\alpha$ -HBCD is the most prominent stereoisomer in the vast majority of aquatic invertebrate and fish samples (Figure 2). The contribution of  $\alpha$ -HBCD was somewhat higher in fish (average 80%) than in invertebrates (average 70%). These findings suggest a transition from sediment/water, where  $\gamma$ -HBCD dominates, to higher organisms (fish and marine mammals/birds) leading to an enrichment of the  $\alpha$ -HBCD stereoisomer. It was suggested that  $\gamma$ -HBCD is metabolized more quickly than  $\alpha$ -HBCD (63, 64), resulting in enrichment of the  $\alpha$ -HBCD isomer (Table SI 3). In a laboratory study, Law and co-workers (63, 64) have measured significant concentrations of  $\alpha$ -HBCD in fish exposed only to either  $\alpha$ -HBCD or  $\gamma$ -HBCD. In both cases, the  $\beta$ -HBCD stereoisomer was formed in the smallest amounts.

**Marine Mammals.** HBCDs have been measured in marine mammals only in a few studies (31, 37, 57, 65–70) to date (Table SI 4). HBCDs were found to bioaccumulate in species feeding inshore (e.g., seals and porpoises). HBCDs could be detected in 131 of 133 marine mammal samples in one study (65). Zegers et al. (65) published data on HBCD concentrations in two species of marine top predators, the harbor porpoise

(*Phocoena phocoena*) and the common dolphin (*Delphinus delphis*), from different European seas. The highest HBCD concentrations were measured in porpoises stranded on the Irish and Scottish coasts of the Irish Sea (median concentration 2900 ng/g lw, maximum 9600 ng/g lw) and the northwest coast of Scotland (5100 ng/g lw). The median concentrations in porpoises from other areas were 1200 ng/g lw on the south coast of Ireland, 1100 ng/g lw on the coasts of The Netherlands, Belgium, and the North Sea coast of France, 770 ng/g lw for the east coast of Scotland, and 100 ng/g lw for the coast of Galicia (Spain). The median HBCD concentrations in the common dolphin, a pelagic marine mammal species feeding primarily over the continental shelf and in offshore waters, were 900 ng/g lw on the west coast of Ireland, 400 ng/g lw in the English Channel coast of France, and 200 ng/g lw in Galicia (65). In comparison, HBCD concentrations in dolphins from the NW Pacific Ocean (Japan) and NE Atlantic Ocean were at the lower end of the range seen in Europe (up to 280 ng/g lw) (66, 67). These concentrations were often similar to, or higher than, the corresponding PBDE levels.

Until now, only a few stereoisomer-specific studies have been performed on marine mammals, and  $\alpha$ -HBCD has been shown to be the dominant stereoisomer (37, 65) (Figure 2). This is in accordance with the dominance of the  $\alpha$ -HBCD isomer in fish, which are the main prey for marine mammals. Additionally, results from in vitro studies using harbor seal liver microsomes have also suggested that  $\alpha$ -HBCD is more resistant to P450-mediated biotransformation than the  $\beta$ - and  $\gamma$ -HBCD stereoisomers (65) and that  $\beta$ - and  $\gamma$ -HBCD may be absent in some species due to their metabolic transformation into hydroxylated analogues.

**Birds.** Only few studies have investigated the occurrence of HBCDs in birds (31, 32, 37, 62, 71–76). HBCDs were found in cormorant liver (*Phalacrocorax carbo*) from The Netherlands (37), in peregrine falcon eggs (*Falco peregrinus*) from Sweden (71), and in guillemot eggs (*Uria aalge*) from areas around the Baltic Sea (73), at concentrations spanning 2 orders of magnitude up to 7100 ng/g lw (Table SI 5). De Boer et al. (75) have determined HBCDs in muscle and liver of peregrine falcons and sparrowhawks (*Accipiter nisus*) from the U.K., with detection frequencies of 30% and 20%, respectively. With the exception of one outlier, these

**TABLE 1. Mean or Median Concentrations and Range of Total HBCDs (ng/g Lipid Weight) in Human Samples<sup>a</sup>**

location	matrix	year	N	N detected	total HBCDs	range	ref
Gothenburg, Sweden	milk	2001	33	12	0.45 (mean); 0.30 (median)	<0.20–2.4	77
Norway	milk	2001	9		0.63 (median)	0.2–2.5	78
Norway	milk	2003–2004	85	49	0.60 (median)	0.4–20	79
Uppsalla, Sweden	milk	2002–2003	30	24	0.42 (mean); 0.35 (median)	<0.20–1.5	80
The Netherlands	cord serum	2003	12		1.7 (mean); 0.32 (median)	<0.16–4.2	81
The Netherlands	maternal serum	2003	78		1.3 (mean); 1.1 (median)	< 0.16–7.0	81
The Netherlands	whole blood	2003	40	1	100 (pg/g whole blood)		82
The Netherlands	serum	2004	91	11	200 (pg/g serum)	<80–360	83

<sup>a</sup> For the calculation of means, values below the LOQ were replaced with the LOQ.

concentrations fell within the range of the other studies. HBCDs were found in 2 out of 40 little owl (*Athene noctua*) eggs from Belgium (72). Low concentrations of HBCDs (<80 ng/g lw) were found in eggs of Arctic birds (31, 76), suggesting that input to the Arctic is predominantly due to long-range transport. Similar to marine mammals, the stereoisomeric profiles of HBCDs were dominated by  $\alpha$ -HBCD although, in some species,  $\beta$ - and  $\gamma$ -HBCD could be detected as well, with a varying pattern of occurrence (Table SI 5).

**Humans and Dietary Intake.** In comparison to PBDEs, much less information is available on the HBCD concentrations in human tissues. Only total HBCDs (by GC) were reported (77–83), and there are no reports of stereoisomer-specific concentrations of HBCDs in human samples (Table 1).

HBCDs were detected in human milk from primiparous Swedish women with the mean and maximum concentrations being 0.45 and 2.4 ng/g lw, respectively (77). HBCDs were also found in Norwegian human milk at concentrations between 0.25 and 20 ng/g lw (78, 79). In general, a low detection frequency for HBCDs in serum/milk samples has been found (Table 1). The HBCD concentrations observed so far in human milk and blood have been lower than total PBDE concentrations but comparable to those of hexabromodiphenyl ethers.

Human exposure to HBCDs occurs through multiple routes. For nonoccupationally exposed persons, the major intake of HBCDs is probably from food and indoor air or dust. The few data available on the HBCD concentrations in commercially purchased Swedish food samples (29) suggest that fish is a major source of dietary HBCD intake (Table SI 6). Considering the high proportion of fish in the Swedish diet, a median intake of 141 ng HBCDs/day was calculated (maximum 1100 ng/day) (84). In addition, HBCD intake through house dust inhalation may also contribute to the overall human exposure, especially considering the high HBCD concentrations present in house dust (Table SI 1). However, the relevance of human HBCD exposure originating from house dust versus food-based HBCD exposure is still unknown.

**Biomagnification of HBCDs.** As shown in Figure 1, levels of HBCDs are often elevated in species at the top of the food chain, which clearly points toward biomagnification. However, only a few studies have specifically investigated the transfer of HBCDs throughout food chains. Increasing concentrations of  $\alpha$ - and  $\gamma$ -HBCD stereoisomers were observed in Lake Ontario in the order mysis, diporeia < forage fish (slimy sculpin, smelt, alewife) < lake trout (54). Biomagnification factors (BMFs), calculated as the ratio between lipid-normalized concentrations in predator and prey species, ranged from 3 to 9 and from 2 to 12 for  $\alpha$ - and  $\gamma$ -HBCD,

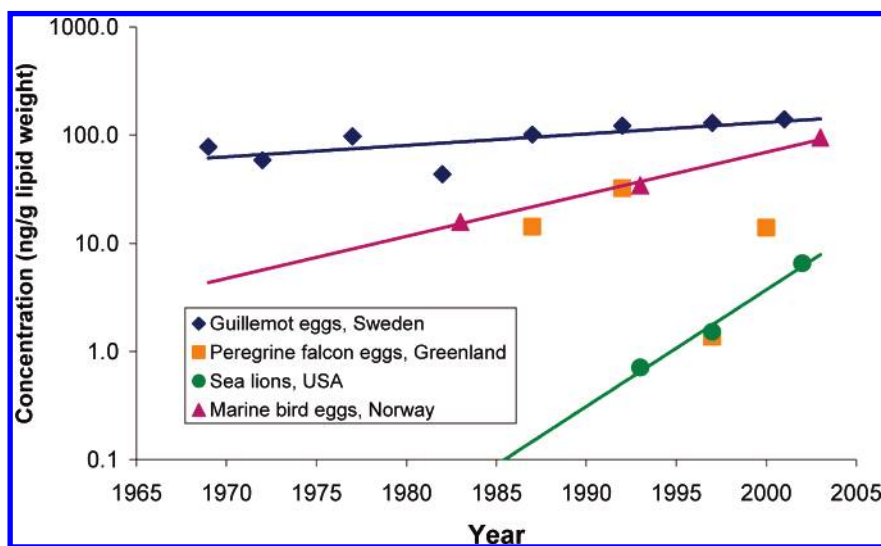
respectively, for the step from forage fish to trout. BMFs for the step from invertebrates to forage fish were lower and ranged from 4 to 6 and from 1 to 4 for  $\alpha$ - and  $\gamma$ -HBCD stereoisomers, respectively. Additionally, an increase in the  $\alpha$ -HBCD to  $\gamma$ -HBCD ratio was observed from invertebrates to forage fish and finally to lake trout. Recently, the biomagnification of HBCDs has also been investigated in a Lake Winnipeg food web (85). Similar BMFs were measured for species belonging to different trophic levels, with the highest values (7 and 11 for  $\alpha$ -HBCD and  $\gamma$ -HBCD, respectively) observed for the step from forage fish (whitefish and white sucker) to predator fish (burbot and walleye).

In the Arctic, HBCDs were found in representative species from the polar bear (*Ursus maritimus*) food chain (57). HBCDs were not found in lower pelagic zooplankton species (*Calanus glacialis*, *Thysanoessa inermis*, and *Paratemisto libellula*), while HBCD concentrations increased with increasing trophic level, with the noticeable exception of the polar bear that appeared capable of metabolizing HBCDs. HBCDs ranged from 5 to 25 ng/g lw in the polar cod (*Boreogadus saida*), from 15 to 35 ng/g lw in the ringed seal (*Phoca hispida*), and from 5 to 15 ng/g lw in the polar bear.

Within the frame of the Swedish environmental monitoring program, HBCDs were measured in herring muscle and guillemot eggs collected from the Baltic Proper. The BMF of total HBCDs for the step between herring and guillemot was 7, while, in the same study, the BMF of sum PCBs for the same step was 20, about a factor of 3 higher (18).

In a food chain from the Western Scheldt estuary, HBCD concentrations were found to increase from invertebrates (shrimp, mussels, worms) to fish (sandeel, the dominant food source for common terns), but decreased from fish to common tern eggs, suggesting that the common tern is able to metabolize HBCDs (62). Similarly to the Lake Ontario food web, an increase in the proportion of the  $\alpha$ -HBCD stereoisomer was found in sandeel and common tern as compared to that of invertebrates and sediment, in which the  $\gamma$ -HBCD stereoisomer was dominant.

In all mentioned studies, the BMFs of  $\alpha$ -HBCD and  $\gamma$ -HBCD stereoisomers in aquatic food webs were >1, suggesting a biomagnification potential for these HBCD stereoisomers. The BMF values were similar to those of some PBDE congeners (BDE 47 and BDE 100) and slightly lower than those of persistent PCBs. Another consistency in all studies was the increasing proportion of the  $\alpha$ -HBCD stereoisomer compared to the  $\gamma$ -HBCD stereoisomer with increasing trophic level in the food web. This is also in accordance with the dominance of the  $\alpha$ -HBCD stereoisomer in marine top predators (marine mammals) (Figure 2). Variations in the solubility and partitioning behavior, as well



**FIGURE 3.** Temporal trends of HBCDs in guillemot eggs from Sweden (73), marine bird eggs from Norway (76), and peregrine falcon eggs from Greenland (32) as well as in sea lions from California, U.S.A. (69). For refs 32, 69, and 73, averaged results over 5 year periods were given, whereas for ref 76, results were averaged over two sites and three species. Exponential regressions of the complete concentration data vs time were significant ( $p < 0.05$ ) for the guillemot eggs, the marine birds eggs, and the sea lions data. The peregrine falcon data did not show a significant change over the observed time period.

as uptake and metabolism of individual stereoisomers, are thought to explain the enrichment of  $\alpha$ -HBCD in aquatic organisms.

**Time Trends.** Studies exploring possible time trends either use data obtained from archived samples or from different studies or they have only few time points. In most cases, data go back only a few years because research interest has been initiated only recently.

One Swedish study (73) on the changes of HBCD concentrations over time in individual and pooled archived guillemot eggs from the Baltic Sea indicated an increase in concentrations between 1969 and 1995 (Figure 3). However, this increase has leveled off between 1995 and 2001, and concentrations of HBCDs seem to have stabilized, whereas PBDE concentrations are decreasing in these samples. A stabilization of HBCD concentrations is not visible in bird egg sampled in the Northern Norway (76). Data from three species and two locations exhibit a remarkably consistent increasing trend since 1983 (Figure 3). In another study, Stapleton et al. (69) have shown an exponential increase in the HBCD concentrations with a doubling time of approximately 2 years in California sea lions stranded between 1993 and 2003 (Figure 3). It is unclear at this time why HBCD concentrations increase in the sea lions, while PBDE levels were highly variable without a significant temporal trend. In male juvenile gray seals from the Baltic Sea sampled in the 1990s, HBCD concentrations were higher compared to those sampled between 1980 and 1985 (70).

In contrast, no time trends could be established for HBCDs either in terrestrial birds (peregrine falcon and sparrowhawk tissues from the U.K. sampled between 1973 and 2002) due to a low detection frequency and biases in sampling (75) or in peregrine falcon eggs from South Greenland sampled between 1986 and 2003 (32) (Figure 3). Interestingly, for this last population, an increase in the levels of PBDEs (10% increase per year) has been observed throughout the investigated time period.

In summary, time trends are not clear yet as the data obtained so far showed either an increasing trend or no significant trend. However, there are no indications available that industry's measures to limit emissions of HBCDs at production and handling sites have led to decreasing concentrations in the environment on a global scale. None of the studies found parallel time trends for HBCDs and

PBDEs. This likely reflects the different regional production and application history for these two BFRs.

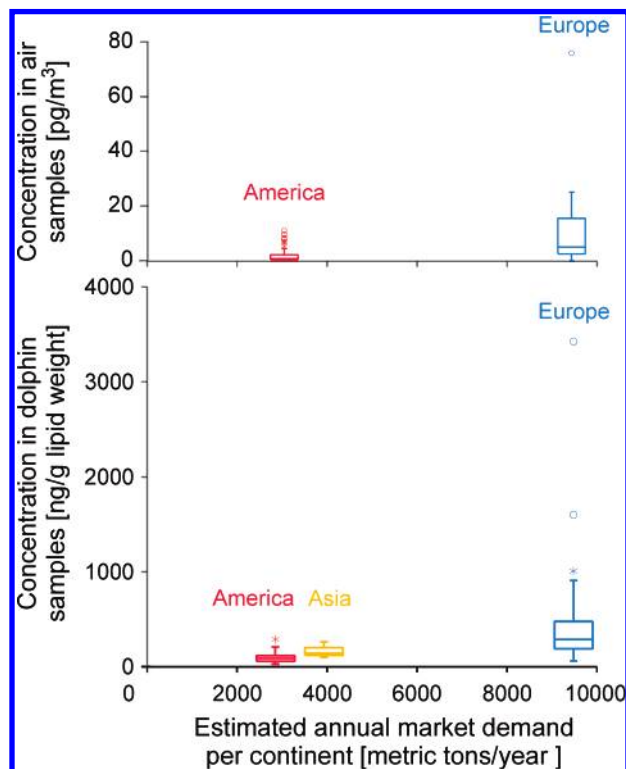
**Geographical Trends.** From the limited data available, three issues are evident:

(1) Concentrations of HBCDs are often elevated by at least 1 order of magnitude in the vicinity of plants either producing or using HBCDs (Figure 1). Several hot spots have already been identified in Europe: the rivers Viskan (Sweden), Tees and Skerne (U.K.), Cinca (Spain), and the Western Scheldt estuary (The Netherlands). All of these sites were related to present or former production facilities for HBCDs or HBCD-retarded materials.

(2) The detection of HBCDs in air samples from remote sites in northern Sweden and Finland and in fish, seals, polar bears, glaucous gulls, and peregrine falcons from Eastern Greenland and Svalbard (25, 31, 32, 57) strongly suggest that HBCDs undergo long-range transport. Although the influence of possible local sources cannot be ruled out completely, the human activities in these areas are probably not sufficient to explain the environmental levels observed. Nevertheless, the importance of the long-range transport of HBCDs via the atmosphere in relation to other sources and transport routes remains to be further established.

HBCD concentrations in air (30), fish (54), dolphins (67), and sea lions (69) from the North American environment appear to be lower than levels in similar samples from Europe (24, 37, 65) (Figure 4). Data from Asia are very scarce. Comparable data exist only for dolphins (Figure 4). In general, the different continental market demand (2) seems to be reflected in different environmental residue levels.

**Enantiomer-Specific HBCD Data.** Six stereogenic centers are formed during the bromination of cyclododecatrienes with the consequence that, theoretically, up to 16 stereoisomers can be resolved in a chiral environment. Therefore, it is very likely that enrichment or discrimination of individual stereoisomers may occur with increasing interactions with biota. Since individual enantiomers can now be resolved on columns with chiral stationary phases (15, 24) the analysis of environmental samples should also use these techniques in the future. With the available chromatographic, crystallographic, and optical rotation data, the six most prominent stereoisomers can now be identified unambiguously (15), not only in technical mixtures, but also in environmental samples. Recently, Janák et al. (24) have reported for the first



**FIGURE 4.** Box plots for total HBCD concentrations in comparable sets of air (29, 30) and dolphin (65–67) samples for America, Asia, and Europe. The position of the box plot on the *x*-axis reflects the estimated annual market demand for HBCDs per continent (2). Two air samples from Europe exhibiting extreme values (280 and 610  $\mu\text{g}/\text{m}^3$ ) were not shown.

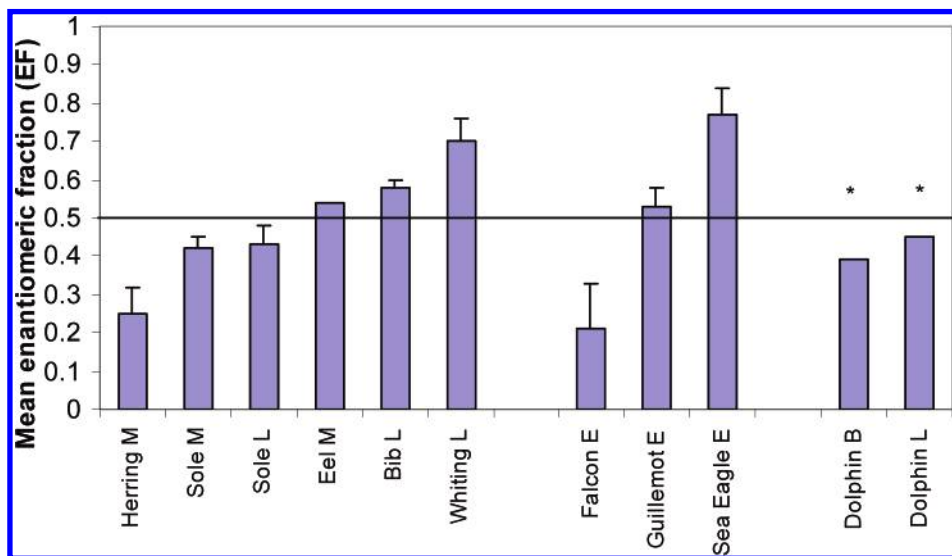
time the selective accumulation of different HBCD enantiomers in marine fish (Figure 5). In two further studies, the database of enantiomeric fractions (EFs) for  $\alpha$ -HBCDs has been extended to herring and several predatory birds (86) and dolphins (67). In all cases, a deviation from the racemic mixture ( $\text{EF} = 0.5$ ) has been observed (Figure 5), suggesting that an enantioselective uptake and/or metabolism of (+)- $\alpha$ -HBCD and (–)- $\alpha$ -HBCD must occur. Interestingly, no clear preference for one or the other  $\alpha$ -HBCD enantiomer was found. Herring muscle and falcon eggs were clearly enriched

in (–)- $\alpha$ -HBCD, whereas in whiting liver and sea eagle eggs, (+)- $\alpha$ -HBCD dominated. We therefore encourage further investigation of the enantiomeric composition of HBCDs in biota for a better understanding of metabolism and the degradation processes affecting HBCDs.

**Data Gaps and Research Recommendations.** It is clear that HBCDs are ubiquitous environmental contaminants. Their levels in species situated at the top of the food chains are now comparable to those of other bioaccumulative chemicals, such as PBDEs. Furthermore, HBCDs show the major characteristics of persistent organic pollutants (POPs): persistency, bioaccumulation, long-range transport, and toxicity. The few time trend studies available to date suggest a slight increase of HBCD concentrations in biota with time. However, this current trend needs to be confirmed by additional studies that should include archived samples (e.g., sample collections) or natural archives (e.g., sediment cores).

Our review shows that there are considerable data gaps in the current literature. A large part of the research on HBCDs has been conducted at locations situated near point sources such as HBCD manufacturing or processing plants, where concentrations in various environmental compartments were found to be relatively high. For a complete understanding of the distribution of HBCDs in the environment, background locations should also be included. More emphasis should be placed upon the terrestrial environment, including humans, for which very limited data are available. Children and their exposure is another priority area for study because, similarly to other persistent organic contaminants, higher exposure during childhood is expected during breastfeeding. Additionally, small children spend most of their day time close to the ground, which results in the ingestion of higher amounts of dust and particles, which have been shown to contain HBCDs. Further, more detailed information about the kinetics, toxicology, pathways of exposure, and bioavailability of HBCDs is needed. More research on possible physiological interactions between different BFRs may be necessary as well as the mode of action of different stereoisomers should be investigated.

Stereoisomer-specific data are also needed to establish profiles and to understand the sources, distribution, and fate of individual stereoisomers. So far, only  $\alpha$ -,  $\beta$ -, and  $\gamma$ -HBCDs have been found in the environment. However, two additional stereoisomers ( $\delta$ -HBCD and  $\epsilon$ -HBCD) have been isolated



**FIGURE 5.** Mean enantiomeric fractions (EFs) for  $\alpha$ -HBCD (calculated as  $\text{EF} = (+)\text{A}/((+)\text{A} + (-)\text{A})$ ; **A** is the peak area corresponding to (+)- $\alpha$ -HBCD and (–)- $\alpha$ -HBCD) and standard deviations for fish (24), birds and herring (86), and dolphins (67). An EF value of 0.5 indicates a racemic mixture. \*, median; L, liver; M, muscle; E, egg; B, blubber.



from technical products (15). Chromatograms of natural samples are usually dominated by  $\alpha$ -HBCD,  $\gamma$ -HBCD, and some traces of  $\beta$ -HBCD. However, small additional peaks are sometimes visible. It remains to be seen if they correspond to additional HBCD stereoisomers that are not yet characterized. In addition, side products or degradation products of HBCDs, which are not yet investigated, are possibly also released into the environment (e.g., tetrabromocyclododecenes). Since degradation of HBCDs occurs in different environmental compartments, formation of HBCD metabolites should be addressed, as well.

Analytical methods with adequate sensitivity based on LC/MS or LC/MS-MS are available for this purpose (87) and should be preferentially used over the determination of total HBCDs by GC/MS. For both methods, the use of  $^{13}\text{C}$ -labeled and  $^2\text{H}$ -labeled HBCDs as internal standards, that compensate for variations in sensitivity during and between sample runs, is essential (23). Due to its lack of stereoisomer specificity, the use of GC in the analysis of HBCDs should be discouraged. If GC is the only alternative, thermal degradation of HBCDs should be minimized through cold on-column injection, short narrow-bore GC columns, thin film stationary phases, and high carrier gas flow rates. An important gap is the lack of harmonized methods for the determination of HBCDs in environmental matrixes. Regular intercalibration studies and participation in laboratory proficiency studies (when available) are important so as to maintain high quality of analytical data. An additional factor is that there are currently no certified reference materials certified for HBCDs that can be used for method validation. Up to now, indicative values for HBCDs have been issued for several reference materials (e.g., lake trout from Cambridge Isotope Laboratories), but the certification of HBCDs in a wider range of environmentally relevant materials is needed.

The risk assessment of HBCDs is not yet completed, but the preliminary conclusions include a statement on the need for further information on HBCDs and/or testing of HBCDs. To improve the quality and breadth of analytical data, we urge that all environmental scientists adopt an LC/MS-based stereoisomer-specific approach for HBCD analysis. This will also assist regulators and risk assessors to evaluate the risks associated with the continuing production and use of this high-production volume chemical.

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## Supporting Information Available

Comprehensive lists of published HBCD concentrations in air, dust, sediment, sewage sludge, wildlife (fish and other aquatic organisms, marine mammals, birds), and human food are presented in Tables SI 1–6. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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